Beta-endorphin grooming in the rat

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β-ENDORPHIN GROOMING IN THE RAT: SINGLE DOSE TOLERANCE

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In rats, intraventricular administration of low doses of ACTH, MSH and fragments of LPH induces display of excessive grooming[3,4,5,7]. This peptide-induced behavior can be suppressed by peripheral administration of specific opiate antagonists (naloxone, naltrexone). As low doses of morphine also induce this behavioral response, it was suggested that part of the behavioral effects of these peptides and morphine may be mediated by a common substrate, presumably involving dopaminergic pathways[12,13]. Recently, it was observed that daily intraventricular administration of $ACTH_{1-24}$ for 10 days did not result in a reduction of the observed grooming behavior[2]. However, a remarkable suppression of the grooming response was observed when a second injection of $ACTH_{1-24}$ was given within 8 h after the first injection[9]. This single dose-induced tolerance was not the result of corticosteroid feedback and could be eliminated by pretreatment with the opiate antagonist naloxone. At this acute level, a cross tolerance of $ACTH_{1-24}$ with β-endorphin, $|D\text{-}Phe^{7}|ACTH_{4-10}$ or morphine was demonstrated[9]. The present study was undertaken to investigate whether there is a similar acute tolerance to β-endorphin grooming.

Male rats of an inbred Wistar strain (140-160 g body weight) received into their foramen interventriculare a plastic canula one week prior to the experimental session. The behavioral procedure consisting of a 15th sec grooming behavior sampling technique has been described previously[4,9]. After intraventricular injection by free hand into the conscious rats, the subjects were placed individually into glass observation boxes and recording of the behavior commenced 15 min thereafter and lasted another 50 min. The maximal possible grooming score therefore is 200. As can be seen in Fig. 1, a single dose of β-endorphin, dissolved in 3 µl saline, induces excessive grooming in the rat. In the figure the amount of saline-induced grooming (30) is subtracted from the value obtained after the peptide injection. The standard error of the mean of saline-induced grooming is represented by the hatched bar. The grooming response is dose-dependent and doses in the range of 100-300 ng already elicit nearly maximal grooming behavior. As was noted before, administration of low doses of β-endorphin not only elicits grooming but also excitation[5]. If higher doses are

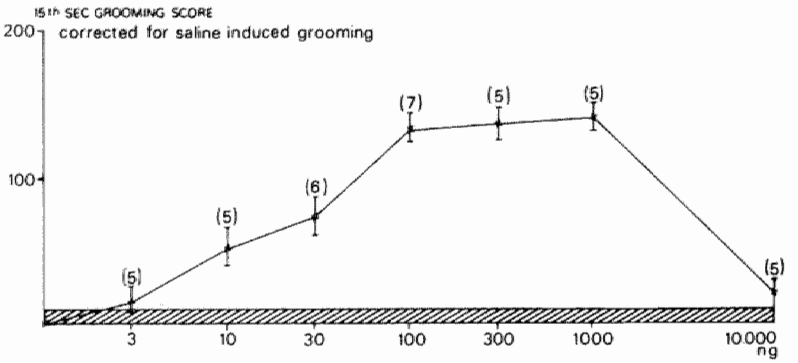

Fig. 1. β-endorphin-induced excessive grooming: dose response curve. ( ) = number of rats

used, grooming is hardly displayed (Fig. 1) but then wet-dog shake behavior followed by a cataleptic state is observed[1,6,8].

If rats first treated with 0.3 µg receive a second injection of β-endorphin (0.3 µg) 24 or 48 or 72 h later, the second injection is as effective as the first one (Fig. 2). However, the response to a second injection is greatly reduced if the interval between the two injections is relatively short. For, 2 and 4 h after the first injection hardly any excessive grooming can be elicited by a second injection with the same dose of β-endorphin. As the interval between the two injections increases, the effect of the first injection slowly dissipates.

In subsequent experiments on the nature of this phenomenon, a 4 h interval

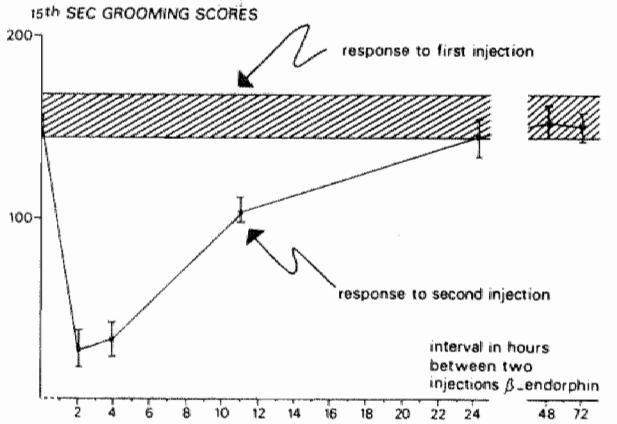

Fig. 2. Single dose tolerance to β-endorphin grooming (0.3 µg/3 µl).

between first and second injection was used. As can be seen in Fig. 3A, it is unlikely that the observed reduction in grooming activity after the second injection can be explained in terms of habituation to the experimental situation as saline/β-endorphin treated rats display a normal grooming response. It could be argued that the interval between the two injections is short enough to allow accumulation of the peptide to a dose sufficient to result in the cataleptic state known to occur when higher doses of morphine or β-endorphin are used[1,8]. However, the data in Fig. 3B indicate that a single dose of 0.6 µg β-endorphin per se is effective in inducing excessive grooming. Furthermore, as was reported for $ACTH_{1-24}$, increasing the dose of β-endorphin used in the second injection overcomes in part the reduction in grooming (Fig. 3B). Thus it seems unlikely that β-endorphin still present from the first injection, can be responsible for the observed loss of effectiveness of the second injection. The results from the last experiments reported here imply that activation of opiate receptors may underly the development of insensitivity of the rats to the second injection with β-endorphin. As Fig. 3C shows, pretreatment with naloxone (1 mg/kg s.c., 5 min prior to the first injection of β-endorphin, 0.3 µg) not only inhibits grooming in the first injection as expected[5], but also prevents the development of acute tolerance to β-endorphin.

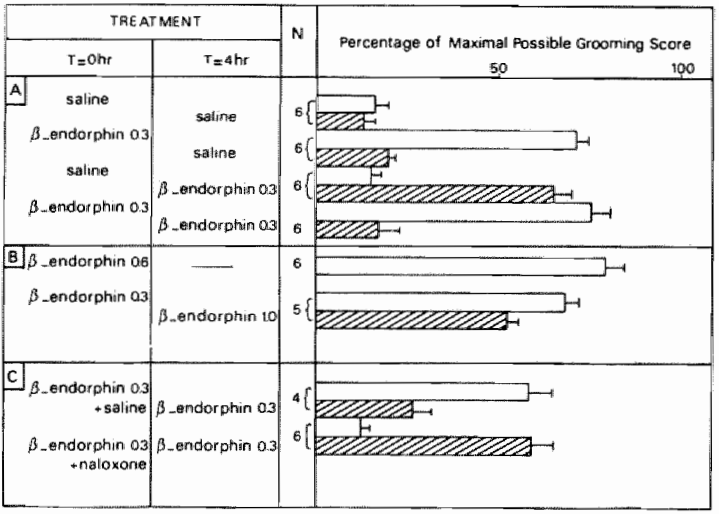

Fig. 3. Naloxone blockade of acute tolerance to β-endorphin grooming.
Open bar : response to first injection ; doses in µg.
Closed bar: response to second injection; doses in µg.

The data presented here are in complete agreement with similar studies on ACTH-induced grooming[9] and once more underscore the notion that fragments of LPH and ACTH, and morphine have a common neural substrate for part of their behavioral effects[12,13]. It is tempting to speculate that the observed reduction of effectiveness of the second injection relates to the acute tolerance which is known to occur to temperature responses to morphine. The time course of both processes seems remarkably similar[10,11]. Since no apparent long term tolerance to β-endorphin (this study) or $ACTH_{1-24}$[2,9] grooming seems to develop, the grooming model may be extremely useful to study the phenomenon of acute tolerance to CNS effects of opiates and opioids.

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